(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient, wherein the biological sample is blood or serum,

wherein the moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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37. (Twice Amended) A method for monitoring the progression of a cancer in a patient comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:311 under moderately stringent conditions;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient, wherein the biological sample is blood or serum;

wherein the moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-6, 8, 9, 11-25, 27-30, and 34-37 are pending, of which claims 1-6 and 13-25 are withdrawn from examination as being drawn to non-elected subject matter. Claims 27-30 and 34-37 have been amended to correct certain typographical errors and to more specifically define the claimed subject matter. Such

amendments have been made without acquiescing to the rejections in the Action. Support for these amendments may be found, for example, at page 20, lines 25-29. No new matter has been added.

Rejection Under 35 U.S.C. § 101

Claims 8, 9, 11, 12, 27-30 and 34-37 stand rejected under 35 U.S.C. § 101 as allegedly lacking utility. More specifically, the Action asserts that these claims are broadly drawn to methods of determining the presence or absence of prostate cancer comprising contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to any one of SEQ ID NOs: 67, 107, 308 and 311; however, the present application fails to provide support for the use of these sequences as specific prostate tumor markers. As to SEQ ID NO:107, the Action asserts that the instant specification provides conflicting information about the expression of this sequence: SEQ ID NO:107 was found over-expressed in 60% of prostate tumors, detectable in normal kidney, and undetectable in all other tissues tested in one instance (citing page 48, lines 10-12 of the present application), but was found highly expressed in 2 prostate tumors and undetectable in all other tissues tested in another instance (citing page 48, lines 25-26 of the present application). As to SEQ ID NO:67, the Action notes that the present application discloses that this sequence was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor (citing page 51, lines 18-20 of the present application). As to SEQ ID NOs:308 and 311, the Action notes that the present application provides that both sequences showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues (citing page 53, lines 9-16 of the present application). Thus, the Action asserts that the instant specification simply supports the fact that SEQ ID NOs:67, 107, 308 and 311 are detectable in many tissues and possibly exclusively in prostate, but does not support the use of these sequences as specific prostate tumor markers to be implemented in the broadly claimed methods.

Applicants respectfully traverse this ground of rejection. Applicants submit that the claimed invention is supported by a specific, substantial and credible asserted utility (*e.g.*, the use of an oligonucleotide that hybridizes to any one of SEQ ID NOs:67, 107, 308 and 311 in detecting prostate cancer). More specifically, with regard to SEQ ID NO:107, Applicants submit

that the present application provides support for over-expression of this sequence in prostate tumors compared to other tissues (including normal prostate tissue) and thus the use of an oligonucleotide that hybridizes to this sequence in detecting prostate tumors. Applicants disagree with the assertion in the Action that the present application provides conflicting information about the expression of this sequence. Rather, the apparent inconsistency in the expression of SEQ ID NO:107 in normal kidney in the above-mentioned two instances is likely the result of different techniques used in characterizing the expression of this sequence. For example, because RT-PCR analysis is generally more sensitive than Northern blot analysis, the detection of the expression of SEQ ID NO:107 in normal kidney by RT-PCR does not necessarily contradict the inability to detect the expression of this sequence in the same tissue by Northern blot analysis. Further still, this point is submitted to be inconsequential as SEQ ID NO:107, being clearly over-expressed in prostate tumors compared to normal tissues, including normal prostate tissue, would be viewed by the skilled artisan as having utility as a prostate-cancer associated diagnostic marker, irrespective of whether low level expression may exist in a non-prostate tissue such as kidney.

Regarding SEQ ID NOs:67, 308 and 311, Applicants submit that the present application provides support for over-expression of this sequence in prostate tissues (including normal prostate and prostate tumors) compared to other tissues and the use of an oligonucleotide that hybridizes to this sequence in detecting prostate tumors in a blood or serum sample from a patient. As noted in the Action, the present application provides that SEQ ID NOs:67, 308 and 311 are over-expressed in prostate tissue and may be used as tissue-specific markers. It is well known to one of ordinary skill in the art that prostate cells are not found in the blood of normal healthy individuals. However, when an individual is afflicted with prostate cancer, the prostate tumor can become invasive, thereby permitting both normal prostate and prostate tumor cells to enter the blood stream. Thus, the presence of either normal prostate or prostate tumor cells in blood or serum of an individual is indicative of the presence of prostate cancer in that individual. Similarly, the presence of either normal prostate or prostate tumor cells in the blood or serum after removal of the prostate in a patient previously diagnosed with prostate cancer is indicative of the presence of residual disease. It is thus not necessary for a marker to be *prostate tumor* specific in order for it to be effective in diagnosing prostate cancer; rather, it is sufficient for the marker to be *prostate* specific. Accordingly, Applicants submit that an oligonucleotide that

hybridizes to any one of SEQ ID NOs:67, 308 and 311 may be used to detect the presence of prostate cancer in a blood or serum sample from a patient, as currently claimed by Applicants.

In view of the above remarks, Applicants submit that this ground of rejections under 35 U.S.C. § 101 has been overcome. Withdrawal of these rejections is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 8, 9, 11, 12, 27-30 and 34-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. More specifically, the Action asserts that because the present application does not have utility, it is not enabled. In addition, the Action asserts that the present application fails to provide disclosure enabling the use of oligonucleotides that hybridize to small fragments of SEQ ID NOs:67, 107, 308 and 311 in diagnostic methods for prostate cancer. The Action also expresses concerns about the possibility that the results from the diagnostic tests of the present invention can be obscured by the presence of excess normal DNA (citing Tascilar *et al.*, *Annals of Oncology* 10: S107-S110, 1999). The Action further cites Tockman *et al.* (*Cancer Research 52*: 2711s-2718s, 1992) to describe considerations necessary for a suspected cancer biomarker to have efficacy and success in a clinical application and to indicate that the art regarding cancer prognosis and life expectancy estimation is highly unpredictable. The Action concludes that the present application is not enabling for the broadly claimed invention and it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Applicants respectfully traverse this ground of rejection. As discussed above, Applicants believe that the lack of utility rejections have been overcome. Accordingly, Applicants submit that the lack of enablement rejection based on the lack of utility rejections has also been overcome.

In addition, Applicants respectfully submit that the Action fails to establish a *prima facie* case of non-enablement in the instant case. With respect to enablement, nothing more than objective enablement is required to meet the requirements of 35 U.S.C. § 112, first paragraph. In particular, as stated by the Board of Patent Appeals and Interferences:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of

> making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Staehelin v. Secher, 24 USPQ 2d 1513, 1516 (B.P.A.I. 1992) (citing *In re Marzocchi* 169 USPQ 367, 369 (C.C.P.A. 1971)) (emphasis original).

In the instant case, the reasonable basis that the specification lacks enablement has not been established in the Action. Although the Action cites two references, these references do not provide sufficient support for doubting that an oligonucleotide that hybridizes to SEQ ID NO:67, 107, 308 or 311 may be used to detect the presence of prostate cancer by detecting the presence and/or levels of expression of the claimed sequences in a suitable biological sample. More specifically, the Tascilar *et al.* reference is directed to detecting oncogene mutations in cells and pancreatic juice to diagnose pancreatic cancer. Although this reference states that "the molecular-based tests should be interpreted with caution, since genetic alterations occurring very early in the pancreatic carcinogenesis do not necessarily prove that a patient will develop invasive malignancy," it does not cast doubt over the use of an oligonucleotide that hybridizes to a nucleotide sequence that is overexpressed in prostate cancer in detecting prostate cancer, much less the prostate cancer-associated sequences specifically claimed by Applicants. As to the concerns related to the source of a sample to be tested in the Tascilar *et al.* reference, Applicants submit that such concerns are also primarily specific to the diagnosis methods described in this reference. For instance, this reference states that "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently, since, for example, K-*ras* mutations are also frequently encountered in other carcinomas, like colorectal carcinoma." To the extent that the presence of excess normal DNA in a sample may obscure the results of diagnostic tests, Applicants submit that it is within the ordinary skill of the art to take necessary precautions when interpreting the results of a particular diagnostic test. For instance, one of ordinary skill in the art would perform the test on control samples (*e.g.*, tissues or cells from a normal individual as a negative control, and tissues or cells from an individual known to have cancer of interest as a positive control) to guide the interpretation of the results of a sample from a test subject.

Applicants further submit that the considerations described in the Tockman *et al.* reference also fail to provide sufficient support for establishing a *prima facie* non-enablement case. Such considerations, which include validation of markers against acknowledged disease end points, establishment of quantitative criteria for marker presence or absence, and confirmation of marker predictive value in prospective population trials, do not provide a reasonable basis for doubting the use of an oligonucleotide that hybridizes to SEQ ID NO:67, 107, 308 or 311 may be used to detect prostate cancer. More specifically, as discussed above, the present application provides support for over-expression of SEQ ID NO:107 in prostate tumors compared to other tissues, which clearly validates SEQ ID NO:107 as a marker for the detection of prostate cancer. In addition, the present application demonstrates over-expression of the other three claimed sequences in prostate tissue compared to other tissues, which allows these sequences to be used as markers for detecting circulating prostate tumor cells in a patient when blood or serum from the patient is used for the analysis. Applicants further submit that both establishing quantitative criteria for the presence or absence of these markers and confirmation of marker predictive values in prospective population trials are within the ordinary skill in the art at the time of the present invention. It is noted that the Tockman *et al.* reference itself, which was published several years before the earliest priority date of the present application, provides certain methods and guidance for establishing quantitative criteria and confirming marker predictive values.

Regarding the assertion in the Action related to hybridization of an oligonucleotide to small fragments of SEQ ID NOs:67, 107, 308 and 311, Applicants note that oligonucleotide probes that hybridize to short fragments of a particular nucleotide sequence (*e.g.*, 20 nucleotides) are routinely used to determine the expression levels of the full length nucleotide sequence, *e.g.*, by RT-PCR, as described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, pp. 14.30-14.33 and throughout Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol. 51*: 263, 1987. Applicants submit that well established protocols provided in these references and others allow the artisan of ordinary skill to use an oligonucleotide that hybridizes to a portion of SEQ ID NO:67, 107, 308, or 311 to characterize the expression level of the corresponding full length nucleotide sequence and thus determine the presence of prostate cancer in a biological sample, as claimed.

In view of the above remarks, Applicants submit that this ground of rejections under 35 U.S.C. § 112, first paragraph, has been overcome. Withdrawal of these rejections is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

All of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 27-30 and 34-37 have been amended as follows:

27. (Twice Amended) A method for determining the presence or absence of prostate cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:67 under moderately stringent conditions; and

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions, relative to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in a patient, wherein the biological sample is ~~selected from the group consisting of:~~ blood~~,~~ or serum ~~and semen~~,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

28. (Twice Amended) A method for determining the presence or absence of prostate cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:107 under moderately stringent conditions; and

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions, relative to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in a patient,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5 X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

29. (Twice Amended) A method for determining the presence or absence of prostate cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:308 under moderately stringent conditions; and

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions, relative to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in a patient, wherein the biological sample is ~~selected from the group consisting of:~~ blood or ~~,~~ serum ~~and semen~~,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

30. (Twice Amended) A method for determining the presence or absence of prostate cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:311 under moderately stringent conditions; and

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions, relative to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in a patient, wherein the biological sample is blood or serum;

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

34. (Twice Amended) A method for monitoring the progression of a cancer in a patient comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:67 under moderately stringent conditions;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient, wherein the biological sample is ~~selected from the group consisting of:~~ blood~~,~~ or serum ~~and semen~~,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

35. (Twice Amended) A method for monitoring the progression of a cancer in a patient comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:107 under moderately stringent conditions;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

36. (Twice Amended) A method for monitoring the progression of a cancer in a patient comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:308 under moderately stringent conditions;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient, wherein the biological sample is ~~selected from the group consisting of:~~ blood~~,~~ or serum ~~and semen~~,

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

37. (Twice Amended) A method for monitoring the progression of a cancer in a patient comprising the steps of:

(a) contacting a biological sample obtained from the patient with an oligonucleotide that hybridizes to SEQ ID NO:311 under moderately stringent conditions;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide under moderately stringent conditions;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient, wherein the biological sample is blood or serum;

wherein the moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5-X SSC overnight;

followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.